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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/436,347	Applicant(s) White And Grillo-Lopez
	Examiner Alana M. Harris, Ph. D.	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-12* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☑ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-12 are examined on the merits.

Specification

2. The use of the trademarks RITUXAN®, PRIMATIZED® and RITUXIMAB® have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

3. The disclosure is objected to because of the following informalities: it contains the incorrect address of the American Type Culture Collection (see page 6); it contains a trademark that is not capitalized (see page 4); and it contains embedded hyperlinks or other forms browser-executable code listed on page 15 that is impermissible and requires deletion (see MPEP 608.01(p)). Applicant is advised to review the entire specification for similar errors.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials. The specification lacks complete deposit information for the deposit of the proprietary CHO cell transfectoma that secretes a chimeric gamma 1 anti-CD20 antibody, also known as RITUXAN®. The specification does not acknowledge whether or not RITUXAN® can be obtained. It is not clear that cell lines possessing the identical properties of the anti-CD20 antibody are known and publicly available or can be reproducibly isolated from nature without undue experimentation. Exact replication of a cell line is an unpredictable event. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and transfectoma species to obtain the claimed antibodies and transfectoma. Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody, a suitable deposit for patent purposes, evidence of public availability of the claimed antibody or

evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

6. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

a. Claims 1 and 12 are broadly drawn to "...an anti-CD20 antibody or fragment thereof". This is broadly interpreted for examination purposes to be any and all anti-CD20 antibodies, no matter the specificity or affinity for the specific epitope on the circulating tumor cells. While the specification is enabling for the application of RITUXAN®, RITUXIMAB® and 2B8-MX-DTPA in the treatment of hematologic malignancies, the specification is not enabling in the application of all other anti-CD20 antibodies, which may have different structural and functional properties. As evidenced by Seaver (Genetic Engineering 14(14):10 and 21, 1994), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be necessary for the antibodies of the claimed passive immunotherapy so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

In addition, Seaver states that "another biological issue with any foreign protein is that the patient can make antibodies to it" (page 21, second full column). As disclosed above in the

rejections under 35 USC 112, first paragraph, the broadly claimed invention encompasses the treatment of humans suffering from a hematologic malignancy. However, the specification has not taught how one skilled in the art would make the necessary chimeric, humanized or human anti-CD20 antibody for use as a human therapeutic, i.e. one that would avoid the formation of antibodies against the foreign mouse antibodies. Further, the specification has not taught what type of carrier or adjuvant would be appropriate for use with the passive immunotherapy, nor what dosages would be effective for the prevention and/or treatment of a hematologic malignancy, such as B-prolymphocytic leukemia (B-PLL) or chronic lymphocytic leukemia (CLL).

Therefore, due the unpredictability of immunotherapeutics in general, as evidenced by Seaver, and in view of the insufficient guidance and/or working examples concerning the use the claimed antibodies as immunotherapeutic agents, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer anti-CD20 antibodies for the treatment and/or prevention of the specified hematologic malignancies without undue experimentation. It would require undue experimentation of one skilled in the art to make and use all anti-CD20 antibodies that would be possibly effective in the treatment of a hematologic malignancy.

Likewise, the recitation "...fragment thereof" implies that a portion of the anti-CD20 antibody, whether it is the heavy or light chain for example would be effective in the treatment of a hematologic malignancy. And would this fragment would be applicable and efficient in recognition of the designated epitope or antigen-binding site for the treatment of a hematologic

malignancy. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl. Acad. Sci. USA 79:1979, 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Panka et al. (Proc. Natl. Acad. Sci. USA 85:3080-3084, 1988) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding Amit et al. (Science 233: 747-753, 1986). Applicant may obviate this "fragment" rejection by adding the recitation "antigen binding fragment".

b. Claims 1 and 12 are broadly drawn to "...administering a therapeutically effective amount...". The claimed invention is not described in such, full clear and concise exact terms to enable any person skilled in the art to make and use the same. "Effective amount" is indefinite when the claims fail to state the function which is to be achieved. The specification does support the rapid reduction of blood tumor cells, rapid tumor lysis, as well as the full remission in one patient. And while the term "therapeutically" modified the term "effective", the specification does not support the use of "administering a therapeutically effective amount an anti-CD20 antibody or fragment thereof" for the broad scope of all the possible therapies, prevention, detection methods that are encompassed by a method of treating. See In re Frederiksen & Nielsen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). Furthermore, claims 1 and 2 do not result in an outcome to be achieved by the method of treating. The claims do not further recite an endpoint indicative of the anticipated results once the method of treatment is implemented. The steps needed for anticipated results are not self-evident. One of skill in the art would not have a reasonable expectation of success in practicing the claimed invention and one skilled in the art would not be able to practice the claimed invention without undue experimentation.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 12 are indefinite for reciting an incomplete method claim which does not clearly set forth method steps and does not include a resolution step which reads back on the preamble of the claimed method.

b. The phrase "effective amount" in claims 1 and 12 is vague and indefinite when the claims fail to state the function which is to be achieved.

c. The recitation "fragment thereof" in claim 1 and 12 is vague and indefinite. It is not clear what is encompassed by the fragment. Is the fragment a portion of the heavy or light chain or absent of a constant region? Accordingly, it is impossible to determine the metes and the bounds of the claimed invention.

d. The recitation "high numbers" as listed in claim 1 is indefinite. It is not clear what is meant by the phrase. Accordingly, it is impossible to determine the metes and the bounds of the claimed invention.

e. Claim 4 is indefinite for reciting "chimeric" as the exact meaning of the word is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to

CDR grafted antibodies. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claim.

f. Claim 8 is vague and indefinite stating the recitation "...chemotherapy, **and/or** lymphokine administration". Is the claim to be read as a Markush group? The applicant is advised to reformat the claim.

g. The recitations "COP" and "CHOP" in claim 11 are vague and indefinite. "COP" and "CHOP" are abbreviations whose identity is not well known in the art. The applicant is advised to amend the claim to include the full terminology.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 4, 7, 8, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Maloney et al. (Blood 90(6):2188-2195, 1997). Maloney et al. disclose a method of treating a hematologic malignancy associated with high numbers of circulating tumor cells that is refractory

to chemotherapy by administering a therapeutically effective amount of an anti-CD20 antibody, formerly art known as IDEC-C2B8 (rituximab) in combination with the chemotherapeutic agent, prednisone, the same as that claimed.

11. Claims 1-4,7, 8, 11 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998). Ford and Donegan disclose a method of treating a hematologic malignancy, leukemia associated with high numbers of circulating tumor cells that is refractory to chemotherapy by administrating a therapeutically effective amount of rituximab (RITUXAN®; formerly IDEC-C2B8), an unconjugated, genetically engineered chimeric murine-human monoclonal antibody directed against the CD20 antigen, the same as that claimed (claims 1,2,4,7 and 12). The specific malignancy directed for treatment was CLL (claim 3). The claimed antibody was administered weekly for about 2 to 10 weeks in combination with chemotherapy, the same as that claimed (claim 8). The rituximab was combined with cyclophophamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy (claim 11).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 5, 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998) and Maloney et al. (Blood 90(6):2188-2195, 1997). The teachings of both, Ford and Donegan and Maloney et al. of a method of treating a hematologic malignancy associated with high numbers of circulating tumor cells that is refractory to chemotherapy by administering a therapeutically effective amount of an anti-CD20 antibody have been discussed in the paragraph above. Ford and Donegan, nor Maloney et al. do not teach the administration of the antibody in the specific dosages set forth in claims 5 and 9.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the anti-CD20 antibody in the recited dosages. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that the dosages of any therapeutic agent must be adjusted and optimized.

14. Claims 1, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatenable over either Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998) or Maloney et al. (Blood 90(6):2188-2195, 1997), in view of Hudziak et al. (U.S. Patent # 5,677,171; 1997). The teachings of Ford and Donegan and Maloney et al. of a method of treating a hematologic

malignancy associated with high numbers of circulating tumor cells that is refractory to chemotherapy by administering a therapeutically effective amount of an anti-CD20 antibody have been discussed in the paragraphs above. Neither, Ford and Donegan or Maloney et al. teach the antibody administered in combination with a lymphokine.

However, Hudziak et al. do teach the simultaneous administration of therapeutically effective amount of antibodies and a therapeutically effective amount of a cytotoxic factor, such as TNF-alpha. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to administer a combination of a lymphokine, such as TNF-alpha and the claimed anti-CD20 antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Hudziak et al. that a cytotoxic factor, such as TNF-alpha exerts it cytostatic (cell growth suppressive) and cytotoxic (cell destructive effect) towards circulating malignant tumor cells of B-PLL or CLL.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris whose telephone number is (703) 306-5880. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Alana M. Harris, Ph.D.
Patent Examiner, Group 1642
February 25, 2000

Yvonne Eyler
YVONNE EYLER, PH.D
PRIMARY EXAMINER